Title: Nasal ketorolac challenge using an acoustic rhinomether in patients with aspirin-exacerbated respiratory disease

Running title: Nasal ketorolac challenge in AERD

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Abstract

Background: Safer and less time consuming alternatives to single-blind placebo-controlled oral challenge (SBPCOC) in order to diagnose aspirin-exacerbated respiratory disease (AERD) have been searched for. Nasal challenges with different non-steroidal anti-inflammatory drugs and assessment methods have been developed.

Objective: Our objective was to evaluate the utility and safety of nasal ketorolac challenge (NKC) using an acoustic rhinomether in patients with suspected AERD

Methods: Thirty-six patients with suspected AERD were included in the study. NKC was performed with placebo (saline) and 13 mg of ketorolac sprayed as aerosol into both nostrils. A positive challenge was defined as an increase of 30% or greater of nasal symptoms recorded by a visual analog scale and a 30 % drop in the sum of both nasal cavities volume at the level of 2 to 8 cm.

SBPCOC with 750 mg of aspirin (in accumulative doses) was carried out in those patients who showed a negative NKC.

Results: Twenty-one patients with suspected AERD had nasoocular reaction during NKC. Four patients of them also developed a mild asthma exacerbations (although only one showed a FEV1 decline >15 %) but no other significative adverse events occurred. The remaining 15 patients who had a negative NKC showed a negative response during aspirin SBPCOC.

Conclusion: NKC assessed by acoustic rhinomether is a reliable method to study patients with AERD. We also suggested that the combination of NKC assessed with acoustic rhinomether was useful a safe in order to select patients suitable to undergo a safe oral aspirin challenge

Key words: Ketorolac, nasal challenge, aspirin exacerbated respiratory disease

Resumen

Antecedentes: El test de exposición simple ciego controlado con placebo (TEC) con aspirina es el patrón–oro para el diagnóstico de la enfermedad respiratoria exacerbada por aspirina (EREA), aunque presenta un riesgo elevado de reacciones durante su realización. Por este motivo, se han desarrollado diferentes procedimientos de provocación nasal con aspirina lisina y ketorolaco.
Objetivo: Evaluar la utilidad y la seguridad del test inhalatorio nasal con ketorolaco (TNK) usando un rinómetro acústico en pacientes con sospecha de EREA

Métodos: Se incluyeron 36 pacientes con sospecha de EREA. El TNK se realizó con placebo (solución salina) y 13 mg de ketorolaco instilado como aerosol en ambas fosas nasales. Un test de exposición positivo se definió como un aumento del 30% o más de los síntomas nasales registrados mediante una escala analógica visual y un descenso mayor del 30% en la suma de ambos volumenes de las cavidades nasales entre 2 a 8 cm del vestíbulo nasal. Si el TNK era negativo, los pacientes se sometían a un TEC con 750 mg de aspirina (en dosis acumulativas).

Resultados: Veintiún pacientes presentaron una reacción nasoocular durante el TNK. Cuatro de ellos presentaron síntomas de asma bronquial (aunque solo uno mostró un descenso del FEV1> 15 %), pero no se produjeron otros acontecimientos adversos significativos. Los 15 pacientes restantes que tuvieron un TNK negative, tuvieron una respuesta negativa durante el TEC con aspirina.

Conclusión: EL TNK evaluado mediante rinómetro acústico es un método fiable para el estudio de pacientes con sospecha de EREA.

PALABRAS CLAVE

Ketorolaco, provocación nasal, enfermedad respìratoria exacerbada por aspirina

Introduction

Definitive diagnosis of aspirin-exacerbated respiratory disease (AERD) only could be realized when a single-blind placebo controlled oral challenge (SBPCOC) with aspirin or any non-steroidal anti-inflammatory drugs (NSAID) was carried out in patients with clinically suspected AERD [1-4]. But, SBPCOC is a time-consuming method which can take at least two days to perform, can result in severe reactions (mainly asthma exacerbations, laryngospasm and even systemic symptoms in some cases), and may require hospital admission, close monitoring and emergency treatment to control respiratory and systemic reactions [5, 6]. Thus, alternative methods have been developed in order to enhance security and lessen time consumption. Bronchial [7] and nasal challenges [8-12] have been developed with different NSAID and assessment methods. In this sense, Lee et al have recently presented a novel method using nasal ketorolac as provoking drug and assessing the nasal response with a peak nasal inspiratory flow (PNIF) meter [8]. Nasal challenge provided a rapid and safe mean of confirming the diagnosis when it induced local reactions in nasal airways in an AERD patients and so, avoided the need of any additional SBPCOC.

The aim of our study was to assess the diagnostic accuracy and safety of nasal ketorolac challenge (NKC) in suspected AERD patients using an acoustic rhinometer (acoR). A positive clinical response during nasal ketorolac challenge would allow to diagnose an AERD patient. But a negative response would also allow to select patients with suspected AERD in order to proceed

with administration of increasing doses of oral aspirin until reaching 750 mg of accumulative dose and thus establish the true negative predictive value of this procedure.

Methods

Patients

Thirty-six consecutive subjects with histories of AERD were studied. All subjects with AERD had moderate-to-severe asthma and a past history of at least one episode of nasoocular reaction, asthma exacerbation or both after NSAID intake [1, 3]. The following data were collected: age, sex, type of NSAID-induced respiratory reactions and the NSAID involved as weel as the existence of bronchial asthma and nasal polyps (Table 1). None of our patients had episodes of urticaria and/or angioedema before controlled challenges and FEV1 values were at least above 70 % of predicted values, with absolute values greater than 1,5 L. Patients with grade 3 or larger polyps were treated, either medically with oral glucocorticoids and fluticasone drops or surgically, to reduce polyp size before nasal challenge; at least 30 days was allowed to elapse between polyp reductive therapy and NKC..

Drugs that could interfere with the results of NKC, such as H1 receptor antagonists and short acting bronchodilator agents , were stopped 1 week and 6 hours before the procedure, respectively. However, all other asthma treatment

(including montelukast, long-acting bronchodilator agents and inhaled glucocorticoids) were not discontinued.

Written informed consent from patients were obtained and the protocol was approved by the Investigation and Ethics Committee of the Hospital .

Nasal ketorolac challenge

All patients were included in a previously established nasal ketorolac challenge (NKC) assessed by acoR (Optomic A1 compact, Barcelona, Spain) [8, 13], at least one month after resolution of the NSAID respiratory reaction . Each patient assessed the symptoms of nasal blockage, rhinorrhea, itching and sneezing, experienced before and after nasal challenge, using a 100 mm visual analogic scale (VAS), with a total range of 0 to 400 mm. Lower respiratory function was also evaluated using a spirometer (SibelMed Lab, Barcelona, Spain). The pre-challenge nasal symptoms of patients recorded by visual analogic scale were showed in Table 2.

An initial single blind challenge with saline as placebo was carried out to rule out nasal hyperreactivity. If the sum of the volumes of both nasal cavities 2-8 cm from the nostril (Vol $_{2\text{-}8}$) after saline declined less than 25 %, the patient underwent nasal challenge reaching a total dose of 13 mg of ketorolac (Laboratorios Vita, Spain) sprayed into both nostrils. 0.9 % fresh saline solution at room temperature was used as placebo. A solution of 10 mg/mL of ketorolac was prepared at the beginning of the procedure by dissolving the content of one

ampoule (of 1 mL of volume) of 30 mg of ketorolac in 2 mL saline. One spray nebulized approximately 0.1 mL , equivalent to 1 mg of ketorolac.

Single-blind challenge was started with saline solution spraying 2 puff into each nostril. Then a graduated challenge with ketorolac solution was performed using an initial dose of 1 mg (1 puff). If no clinical response occurred and if Vol $_{2\text{-}8}$ declined less than 30 %, incremental doses of ketorolac were administered every 30 minutes controlled with acoustic rhinometry and spirometry before each dose: 2 mg (1 spray for each nostrils), 4 mg (2 sprays for each nostrils) and finally 6 mg (3 sprays for each nostrils). Thus, the maximal accumulative doses in nasal challenge was 13 mg of ketorolac. If patient showed any symptoms or signs during incremental ketorolac exposure, the challenge was interrupted and the reaction treated.

A positive nasal challenge was defined as a) an increase of 30% or greater of the total nasal symptoms recorded by VAS and b) 30 % or greater decline in the nasal airway measured by Vol $_{2\text{-}8}$ comparing with that obtained after saline solution instilation. Lower airways signs and symptoms, such as asthma exacerbation or laryngeal spam, were also recorded if any. A 15 % decline in basal FEV1 values during NKC was considered as a positive asthmatic response. A laryngeal spam was defined as crowing sounds over trachea with and amputated inspiratory loop in the flow/volume curve.

A negative nasal challenge response was defined when no symptoms or a decrease of <30% in Vol $_{2\text{-}8}$ were observed or when no change in nasal

volume or an increase <30% measured by VAS were occurred in a 3 hour-period after the instillation of the last dose of nasal ketorolac.

Oral aspirin challenge

All patients with suspected AERD, but negative NKC were included in a previously established 3-day single-blind placebo-controlled oral aspirin challenge [6]. Oral aspirin challenge was performed at least 1 week after a negative NKC result was obtained in suspected AERD patient and after withdrawal of montelukast at least 5 days before, in order to avoid the possibility of a silent desensitization [14]. The first day of placebo challenges was done to ensure airway stability with pulmonary function measured after each observation period (the variability of FEV1 will be less than 10 percent from baseline).. The first 2 aspirin doses (50 and 100 mg) were administered on day 2, and the remaining doses (250 and 500 mg) were administered on day 3. Placebo and aspirin were administered in opaque gelatin capsule at 180 minutes interval between each dose.

Challenge was considered positive if it fulfilled at least one of the following criteria: pruritus and wheals; macular and/or papular areas in any location, swelling of skin and/or external mucosa and nasoocular and/or lower airways signs and symptoms, including bronchospasm with a fall in FEV1 > 15 percent or laryngospam. The clinical characteristics of each SBPCOC (symptoms, dose and elapsed time) were recorded. During challenge procedure, patients were clinically monitored at 15 minutes, 30 minutes and

every hour after administering each NSAID or placebo dose, or at any time when symptoms were referred by the patient.

Results

Nasal ketorolac challenge

During study, NKC were carried out in 36 consecutive patients with suspected AERD. Twenty-one patients had a positive NKC reaction with isolated nasal and ocular symptoms (Table 3). Four of them also developed lower respiratory tract symptoms, including mild bronchospam and/or chest tightening which were treated with SABA and oral glucocorticoids. The fall in FEV1 values during NKC in patients with asthmatic symptoms were 17.83 %, 8.96 %, 5.46% and 12.26 % in patient number 1, 14, 15 and 18, respectively. No significative changes in FEV1 values were observed in patients who had nasoocular reaction alone. Twelve patients who reacted during NKC after exposure to 13 mg of ketorolac (57 % of cases), 3 patients at 1 mg, 4 at 3 mg and 2 at 7 mg of ketorolac.

A post-hoc analysis was also performed to compare the differences in clinical reaction in relation to ketorolac doses in four patients (number 9, 10, 11 and 22) who were successfully desensitized with aspirin due to suboptimal control of nasosinusal symptoms and anosmia and who were twice challenged with nasal ketorolac during the process (Table 4). The Vol $_{2\text{-}8}$ values obtained during first clinical reaction and the provoking dose of ketorolac were not significantly different than those observed in a subsequent challenge.

The remaining 15 patients with suspected AERD had no clinical reaction during NKC and underwent an additional controlled oral challenge in order to confirm or to discard AERD.

Oral aspirin challenge

Fifteen patients who had a convincing history of AERD, but negative NKC were underwent SBPCOC with aspirin and they tolerated aspirin 750 mg in accumulative dose (see Table 3).

Discussion

The existence of moderate-to-severe, unstable and poorly controlled asthma who often exhibited AERD patients, induces many clinicians to bypass an oral challenge with NSAID due to increased adverse reaction risk and to the fact that it is time consuming. Therefore, outside of research units, NSAID challenges are rarely performed for diagnostic purposes [2-4, 6].

We have demonstrated that using NKC assessed with acoR was a safe, effective and reproducible method to diagnose AERD. Unlike oral challenges, NKC caused fewer adverse extrapulmonary effects and bronchospasm, and predominantly induce isolated nasoocular reactions. With the exception of one patient who developed asthma symptoms with > 15% drop in FEV1 no other severe adverse events occurred. In addition, all of our patients continued with their asthma treatment (including montelukast, a leukotriene modifier drug) during the NKC decreasing the likelihood of severe lower respiratory reactions without significantly masking nasoocular symptoms [15]. Our patients experienced the symptoms at 49 minutes of mean between 2 and 4-fold accumulative doses of ketorolac in 85% of cases.

Our study also explored the capacity of NKC assessed by acoR to predict the oral aspirin challenges responses. We showed that a negative nasal response to 13 mg of ketorolac (in accumulative dose) is always followed by a negative response during aspirin oral challenge in every instances studied in our group of patients. This finding would allow the clinician to perform a SBPCOC with aspirin with the certainty of a safe outcome and possibly shorter

protocols. In a recent study though, up to 10% of patients with a negative NKC had respiratory reactions during a subsequent oral aspirin challenge. They evaluated 100 patients with AERD (by clinical history and positive oral aspirin challenge) who were rechallenged with intranasal ketorolac [8]. Ninety percent experienced positive reactions (defined as rhinitis, conjunctivitis, and/or bronchospasm with a significant decrease in PNIF rate and/or FEV1 values). These previous observations have been also confirmed in a recent study which evaluate the feasibility of PNIF as an objective measurement in the assessment of a reaction to nasal ketorolac. [9] The fact that in our group all patient tolerated an aspirin challenge after a negative NKC could be due to the use of acoR instead of nasal peak flow meter. Recently, Miller at al have also described a high percentage of patients (45%) with a positive oral challenge with 325 mg of aspirin who had a previous negative aspirin-lysine acoR-monitored nasal challenge suffered [10]. Anterior active rhinomanometry as objective assessment method has also been previously used and it showed that only sixteen of 20 oral challenge-proven AERD patients (80%) had a positive nasal response response [11] to the nasal challenge with lysine-aspirin. These different clinical outcomes could suggest that the NSAID used, the objective method to measure the changes in nasal airways or both might have relevance in the results of nasal NSAID challenges.

In conclusion, NKC assessed by acoR was characterized by a lower incidence of side effects during the procedure, and, although the sample size presented here was not large enough to fully determine the negative predictive value of acoustic rhinometry, our data also seems to suggest that the

combination of NKC assessed with acoR was safe and useful procedure in order to select patients suitable to undergo a safe oral aspirin challenge.

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Table 1. Clinical characteristics of AERD patients

Case	Sex	Age	Nasal polyps	Type of NSAID reaction	NSAID involved
1	M	48	Yes	BA	Ibu, Met
2	M	67	Yes	NOR + BA	Ket
3	F	65	No	NOR + BA	ASA, Met, D, Ket, Ibu
4	F	67	Yes	BA	ASA
5	M	70	Yes	NOR + BA	ASA
6	M	45	Yes	NOR	ASA
7	M	28	Yes	BA	ASA
8	F	54	Yes	NOR+ BA	ASA
9	F	52	Yes	BA	ASA, Ibu
10	M	56	Yes	NOR + BA	ASA, Met
11	F	41	Yes	NOR + BA	ASA, Ibu
12	F	68	Yes	BA	Ibu, Met
13	M	71	Yes	BA	Ibu
14	F	59	Yes	NOR + BA	ASA, Met, Ibu
15	M	51	Yes	NOR	ASA, Ibu
16	M	52	Yes	BA	ASA
17	M	53	Yes	NOR + BA	Ibu, Met
18	F	46	Yes	NOR + BA	ASA, Met

AERD, Aspirin-exacerbated respiratory disease;

NSAID, non steroidal anti-inflammatory drugs

M, male; F, female.

ASA, aspirin; D, diclofenac; Ibu, ibuprofen; Ket, ketoprofen; Met, metamizol.

NOR, nasoocular reaction; BA, bronchial asthma

Table 1. Clinical characteristics of AERD patients (continuation)

Case	Sex	Age	Nasal polyps	Type of NSAID reaction	NSAID involved
19	F	37	Yes	NOR + BA	ASA, Met
20	F	37	Yes	BA	ASA
21	M	51	Yes	NOR + BA	Ibu
22	F	55	Yes	NOR + BA	ASA, Met, Ibu, D
23	M	17	No	BA	Ibu, P
24	F	58	No	NOR + BA	Ibu
25	F	40	Yes	NOR + BA	ASA
26	F	37	No	NOR	D
27	F	31	No	BA	ASA, Ibu, P, Met
28	M	22	Yes	NOR+ BA	ASA, Ibu
29	M	54	No	BA	Ibu, K, D
30	M	36	Yes	NOR	Ibu
31	F	32	Yes	NOR + BA	Ket
32	F	43	No	NOR + BA	ASA, Ibu, Ket
33	F	39	No	BA	Ibu, Met
34	F	59	Yes	NOR	ASA, Met, Ibu
35	F	46	Yes	BA	Met
36	F	37	No	BA	ASA

AERD, Aspirin-exacerbated respiratory disease;

NSAID, non steroidal anti-inflammatory drugs

M, male; F, female

NOR, nasoocular reaction; BA, bronchial asthma

ASA, aspirin; D, diclofenac; Ibu, ibuprofen; K, ketorolac, Ket, ketoprofen; Met, metamizol; P, paracetamol

Table 2. Basal nasal symptoms of patients recorded by visual analogic scale

Case	Nasal blockage	Rhinorrea	Itching	Sneezing	Total nasal score
1	81	35	12	41	229
2	65	52	11	27	155
3	63	66	53	68	250
4	21	54	21	61	157
5	66	48	18	52	184
6	32	71	0	41	144
7	54	39	22	66	181
8	59	57	10	42	168
9	47	52	18	18	135
10	83	70	0	31	184
11	77	51	22	56	206
12	56	40	31	25	152
13	58	45	41	50	194
14	80	0	20	0	100
15	70	75	0	0	145
16	49	22	0	25	96
17	72	76	0	78	226
18	68	68	12	40	188
19	75	56	21	32	184
20	79	54	31	76	240
21	69	67	40	40	216
22	88	75	61	62	286
23	55	52	61	48	216
24	50	50	38	36	174
25	72	67	0	21	160
26	49	51	0	38	138
27	61	60	12	22	155
28	85	70	67	80	302
29	44	31	28	20	123
30	85	36	0	36	157
31	81	67	21	44	213
32	69	56	10	21	156
33	56	39	0	31	126
34	65	58	0	33	156
35	51	60	0	12	123
36	21	30	0	0	51

Table 3. Results of nasal ketorolac challenge in AERD patients

Case	Provoking accumulative dose (in mg)	Elapsed time (in min)	Vol_{2-8} decline (in percent)	Respiratory symptoms	Result
1	13	45	34.6	NOR + BA	Positive
2	13	180	16		Negative
3	1	30	53.7	NOR	Positive
4	7	30	34	NOR	Positive
5	13	180	10.2		Negative
6	13	50	33.8	NOR	Positive
7	13	180	6.5		Negative
8	13	180	15.7		Negative
9	3	20	39	NOR	Positive
10	13	55	45	NOR	Positive
11	13	30	40.5	NOR	Positive
12	13	180	15.4		Negative
13	13	180	13.7		Negative
14	3	20	32.8	NOR + BA	Positive
15	13	120	49.7	NOR + BA	Positive
16	13	55	31.6	NOR	Positive
17	13	40	30.3	NOR	Positive

NOR, nasoocular reaction; BA, bronchial asthma

$Vol_{2-8,}$ the sum of the volumes of both nasal cavities 2-8 cm from the nostril

Table 3. Results of nasal ketorolac challenge in AERD patients (continuation)

Case	Provoking accumulative dose (in mg)	Elapsed time (in min)	Vol_{2-8} decline (in percent)	Respiratory symptoms	Result
18	13	90	55.4	NOR + BA	Positive
19	13	50	30.9	NOR	Positive
20	1	30	36.6	NOR	Positive
21	7	20	30.4	NOR	Positive
22	13	60	49.9	NOR	Positive
23	13	180	18.9		Negative
24	13	180	12.3		Negative
25	13	180	7.4		Negative
26	13	180	13.4		Negative
27	13	90	33.5	NOR	Positive
28	3	30	30.3	NOR	Positive
29	13	180	6.8		Negative
30	13	180	15.6		Negative
31	3	30	53.5	NOR	Positive
32	1	30	45.4	NOR	Positive
33	13	180	19.2		Negative
34	13	120	30.8	NOR	Positive
35	13	180	12.1		Negative
36	13	180	1.9		Negative

NOR, nasoocular reaction; BA, bronchial asthma

$Vol_{2-8,}$ the sum of the volumes of both nasal cavities 2-8 cm from the nostril

Table 4. Reproducibility of response to nasal ketorolac challenge in four patients with AERD

Case	Ketorolac provoking dose (in mg)	Vol_{2-8} decrease after clinical reaction[1]	
		First NKC	Second NKC[2]
9	3	39.0	31.8
10	13	45.0	48.4
11	13	40.5	31.6
22	13	49.9	41.3

$Vol_{2-8,}$, the sum of the volumes of both nasal cavities 2-8 cm from the nostril

NKC, nasal ketorolac challenge

[1] Maximum decline in the nasal airway measured by Vol_{2-8} compared with that obtained after saline solution instillation (in percent).

[2] The elapsed time between first and second nasal ketorolac challenge was at least 6 months for each patient.